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The Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT) Trial

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OBJECTIVES The purpose of the SCANDSTENT study was to evaluate the use of sirolimus-eluting stents (SES) in complex coronary lesions.

BACKGROUND The use of SES improves angiographic and clinical outcomes compared with bare-metal stents (BMS) in simple coronary artery lesions, but there is limited evidence of their safety and efficacy when implanted in complex lesions.

METHODS We randomly assigned 322 patients with symptomatic complex coronary artery disease to receive either SES or BMS. The lesions were occluded (36%), bifurcational (34%), ostial (22%), or angulated (8%) in morphology. The primary end point was the difference in minimal lumen diameter six months after stent implantation.

RESULTS The patients were well matched in terms of demographic and angiographic baseline characteristics; 18% had diabetes. The reference vessel diameter was 2.86 mm in mean, and the lesion length 18.0 mm. At follow-up, patients who received SES had a minimal lumen diameter of 2.48 mm compared with 1.65 mm in those who received BMS ($p < 0.001$), a diameter stenosis of 19.3% versus 43.8% ($p < 0.001$), and 2.0% versus 31.9% developed restenosis ($p < 0.001$). The rate of major adverse cardiac events was 4.3% with SES versus 29.3% with BMS ($p < 0.001$), and stent thrombosis was observed in 0.6% in the SES group versus 3.1% in the BMS group ($p = 0.15$).

CONCLUSIONS The use of SES markedly reduced restenosis and the occurrence of major adverse cardiac events in patients with complex coronary artery lesions without increasing the risk of stent thrombosis. (J Am Coll Cardiol 2006;47:449–55) © 2006 by the American College of Cardiology Foundation

Compared with balloon angioplasty, stent implantation in coronary artery lesions improves procedure safety but increases neointimal hyperplasia in the treated vessel, especially in the presence of diabetes mellitus and complexity of the treated lesion (1–8). Previous attempts to reduce the formation of neointimal hyperplasia with local and systemic pharmaceutical drug therapy have not been successful (9–11), until recently, when two polymer-based anti-inflammatory drugs were shown to reduce the rate of restenosis in simple coronary artery lesions (12–16). Because patients with complex lesions such as occluded, bifurcational, ostial, and angulated lesions have been excluded from previous trials, there is uncertainty as to whether implantation of drug-eluting stents can be performed safely and efficiently in such complex lesions. We performed the randomized Stenting Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) trial to evaluate the clinical and angiographic outcome after implantation of either sirolimus-eluting stents (SES) or bare-metal stents (BMS) in patients with complex coronary artery lesions.

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METHODS

Patients and study design. The study was a randomized trial conducted at four cardiology centers in Denmark. Patients were considered eligible if they were older than 18 years of age, had stable or unstable angina or a recent non–ST-segment elevation myocardial infarction, and had one or more de novo lesions in native coronary vessels between 2.25 and 4.50 mm in diameter with one of the following characteristics: occlusion with a length of ≥15 mm (interrupted contrast filling, Thrombolysis In Myocardial Infarction flow grade 0 or 1), bifurcation (side branch >1.75 mm in diameter to allow balloon dilatation with a minimum risk of severe dissection), ostial location (≤5 mm from the ostium), or angulations (>45° within the lesion). Major clinical exclusion criteria were a life expectancy of <1 year, allergy to any of the pharmaceuticals used, and myocardial infarction less than three days before the procedure. Angiographic exclusion criteria were: 1) lesions located in unprotected left main stem coronary arteries and bypass grafts, and 2) lesions containing visible thrombus. The protocol was approved by the ethics committee of Copenhagen and Frederiksberg, and all patients provided written informed consent.

Patients were pretreated with aspirin (75 mg) and clopidogrel (300 mg), and heparin was administered to maintain an activated clotting time of >250 s during the procedure.

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Abbreviations and Acronyms

BMS = bare-metal stent
LL = late (lumen) loss
MLD = minimal lumen diameter
SES = sirolimus-eluting stent
TLR = target lesion revascularization

Glycoprotein receptor antagonists were used at the discretion of the operator. Cardiac enzymes were measured before and 16 to 24 h after the procedure, and 12-lead electrocardiograms were obtained before the procedure and before discharge from the hospital. Aspirin and clopidogrel were continued indefinitely and for one year after stent implantation, respectively.

Clinical follow-up was performed continuously for seven months, and a repeat coronary angiography was scheduled after six months. In case recurrent symptoms required a nonscheduled angiogram within three months after stent implantation that did not result in revascularization of the target lesion, another angiography was performed as scheduled. A nonscheduled angiogram performed three to six months after stent implantation replaced the six-month angiogram.

Randomization and stent implantation. Randomization was performed (1:1) by computerized assignment with stratification with regard to gender and the presence of diabetes. The lesions were treated by standard percutaneous interventional methods avoiding debulking techniques. The BMS Bx Velocity stent mounted on the balloon expandable delivery system, Sonic (Cordis/Johnson & Johnson, Warren, New Jersey) or the SES Bx Velocity stent with sirolimus-eluting properties, Cypher (Cordis/Johnson & Johnson), were implanted in the lesions under high pressure (>12 atm). Implantation of more than one stent was allowed to cover the entire lesion, and side branch stent implantation was performed at the discretion of the operator. Both operator and patient were aware of the assigned treatment.

Quantitative coronary angiography. Coronary angiograms were acquired in identical orthogonal projections after an intracoronary injection of 0.2 mg of nitroglycerin before, immediately after, and six months after stent implantation. All angiograms were analyzed by an independent core laboratory whose technicians were blinded both with regard to the type of stent implanted and to the clinical outcome of the patients using the Medis computerized edge-detection system (Medis, Nuenen, the Netherlands) (17). The reference diameter in ostial lesions and side branches of bifurcations was determined immediately distally to the lesion. Binary restenosis was present whenever the diameter stenosis was ≥50 %. Late lumen loss (LL) was determined as the change in minimal lumen diameter (MLD) from immediately after stent implantation to follow-up. Angiographic findings were recorded both inside the stent (in-stent) and in the vessel area within 5 mm of its borders (in-lesion).

Study end points. The primary end point of the study was the difference in MLD in the target lesion at follow-up as determined by quantitative coronary angiography and analyzed by the independent core laboratory, the main branch being the "target" area of the bifurcational lesions. Secondary end points were LL, the rate of binary restenosis, percent diameter stenosis at the six-month angiography, and the rate of major adverse cardiac events occurring within seven months after treatment: death, myocardial infarction, or target lesion revascularization (TLR).

A non–Q-wave myocardial infarction during or after the intervention was defined as a total creatine kinase elevation two times or greater than the upper normal limit with a concomitant increase in creatine kinase-myocardial band blood concentration in the absence of pathologic Q waves. A Q-wave myocardial infarction was defined as the development of new Q waves lasting ≥0.4 s in two or more contiguous leads together with clinical signs of a myocardial infarction (chest pain or increase in the creatine kinase-myocardial band).

Target lesion revascularization was defined as repeat revascularization (percutaneously of the target lesion or surgical of the vessel containing the target lesion). Revascularization should be performed in the presence of documented ischemia and a significant stenosis of the lesion.

Stent thrombosis was defined as definite in case of angiographically visible signs of a contrast filling defect in the target lesion in connection with an acute coronary syndrome. A possible stent thrombosis was present in case of a sudden and unexpected death during the observation period. Acute, subacute, or late thrombosis occurred within 24 h, within 1 month, or during the succeeding 12 months after stent implantation, respectively.

Statistical analysis. With a power of 80% and a two-sided type 1 error of 0.05, we calculated that 125 patients in each group would have to complete the study to detect a 0.25-mm increase in MLD at follow-up from an expected average of 1.64 mm in the BMS group (12) to 1.89 mm in the SES group with a standard deviation of 0.70 mm. With an expected 15% rate of attrition ≥150 patients had to be included in each arm of the study. With a similar number of patients a reduction in the rate of major adverse cardiac events from 30% (12) to 18% could be detected.

Differences in categorical variables between the two groups were analyzed using the chi-square test or the Fisher exact test whenever numbers in a category were <5. Continuous variables were analyzed using the Kaplan-Meier method and the log-rank test. All p values were two-sided. Subgroup analyses were performed by calculating odds ratios for the risk of TLR in patient groups according to age, gender, and lesion located in the left anterior descending artery, in addition to those previously demonstrated to be

Table 1. Baseline Characteristics of Patients and Lesions

	Sirolimus-Eluting Stent (n = 163)	Bare-Metal Stent (n = 159)	p Value
Age (yrs)	62.9 (9.2)	62.5 (9.4)	0.94
Male gender (%)	74	79	0.30
Diabetes (%)	18	18	0.90
Hypertension (%)	46	38	0.21
Hyperlipidemia (%)	81	84	0.46
Current smoking (%)	36	33	0.82
Family predisposition (%)	45	44	0.91
Previous myocardial infarction (%)	54	50	0.58
Unstable angina (%)	25	26	0.70
Left ventricular ejection fraction (%)	54 (12)	55 (10)	0.56
Previous PCI/CABG (%)	19	16	0.69
Multivessel disease (%)	43	45	0.29
Target lesion coronary artery (%)			
LAD	45	53	0.31
LCX	25	23	
RCA	30	24	
Lesion length (mm)	18.8 (13.0)	17.2 (11.1)	0.43
Lesion type (%)			
Occlusion, n = 115	36	35	0.94
Bifurcation, n = 109	35	33	
Ostial, n = 73	21	24	
Angulation, n = 25	7	8	

Numbers are mean values with SD in parentheses.

CABG = coronary artery bypass grafting; LAD = left anterior descending; LCX = left circumflex; PCI = percutaneous coronary intervention; RCA = right coronary artery.

associated with increased restenosis: presence of diabetes, long lesions, and lesions located in small vessels.

Bonferroni adjustment for multiple comparisons was used. We calculated cumulative frequency distributions of the quantitative angiographic measurements before and after percutaneous coronary intervention and at follow-up.

RESULTS

Procedural and patient characteristics. From October 2002 to June 2004, 322 patients were enrolled in the SCANDSTENT trial. The procedural success was 99.4% in the group receiving SES and 98.7% in the BMS group (p = 0.91). The data of three patients were precluded from the analyses because of technical issues. In two other patients, the stent could not be inserted into the lesion, and alternative stents were succesfully used; the data of these two patients have been analyzed along with the others (according to the intention-to-treat principle).

The clinical baseline characteristics of the two patient groups were well matched, and no differences were found in baseline angiographic characteristics (Table 1). Seventy-two patients had a lesion with more than one complexity. We implanted 1.4 versus 1.3 stent per patient in the SES versus the BMS group (p = 0.89) with a total stent length of 26.1 mm versus 22.6 mm (p = 0.60), respectively. Glycoprotein IIb/IIIa inhibitors were used in 33% of patients in the sirolimus and 31% in the bare-metal stent group (p = 0.96). The reference diameters of side branch bifurcations were 2.22 mm and 2.18 mm (p = 0.55). Stents were implanted in 55% and 53% of side branches in the two groups (p = 0.75) using "Y"-, "T"-, and "crush" techniques with similar frequences in the two groups. Side branch treatment after stent implantation in the main branch was always finalized with a "kissing balloons" maneuver.

Quantitative coronary angiography analysis. Follow-up coronary angiography was available in 292 (91%) of the patients. Figure 1 shows the cumulative frequency curve of MLD before, immediately after, and at six months after stent implantation. In Table 2, the results of the angiographic analyses are shown, including the main branch of the bifurcations. The restenosis rate in side branches was

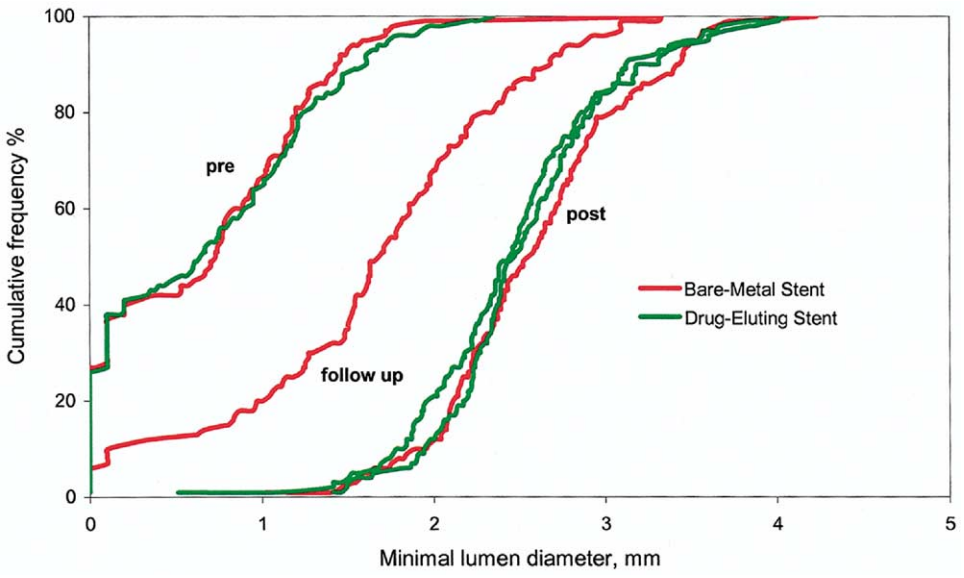

Figure 1. Cumulative frequency of the minimal lumen diameter before (pre), immediately after (post), and six months after (follow-up) stent implantation in patients who received sirolimus-eluting and bare-metal stents.

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Table 2. Quantitative Coronary Angiography*

	In-Lesion Zone			In-Stent Zone		
	Sirolimus-Eluting Stent (n = 62)	Bare-Metal Stent (n = 157)	p Value	Sirolimus-Eluting Stent (n = 162)	Bare-Metal Stent (n = 157)	p Value
Reference vessel diameter (mm)	2.86 (0.53)	2.87 (0.48)	0.49	2.86 (0.53)	2.87 (0.48)	0.49
Minimal lumen diameter (mm)						
Before procedure	0.71 (0.67)	0.67 (0.62)	0.71	0.71 (0.67)	0.67 (0.62)	0.71
After procedure	2.52 (0.51)	2.58 (0.56)	0.27	2.60 (0.48)	2.66 (0.53)	0.21
At 6-month follow-up	2.48 (0.58)	1.63 (0.82)	<0.001	2.58 (0.59)	1.65 (0.82)	<0.001
Diameter stenosis (%)						
Before procedure	75.9 (22.2)	77.4 (20.1)	0.53	75.9 (22.2)	77.4 (20.1)	0.53
After procedure	15.1 (9.0)	14.0 (10.1)	0.19	12.8 (7.4)	11.6 (8.3)	0.08
At 6-month follow-up	19.3 (12.8)	43.8 (26.1)	<0.001	16.4 (11.4)	43.1 (26.3)	<0.001
Late lumen loss (mm)	0.04 (0.50)	0.94 (0.74)	<0.001	0.02 (0.42)	1.01 (0.75)	<0.001
Binary (>50%) restenosis (%)	3 (2.0)	46 (31.9)	<0.001	3 (2.0)	44 (30.6)	<0.001

Numbers are mean values with SD in parentheses. *Only main branches of bifurcations.

reduced from 42% to 15% ($p < 0.001$). At follow-up, MLD was significantly larger and the diameter stenosis smaller, resulting in a 0.04 mm LL in patients who were treated with SES compared with 0.94 mm in those who received BMS (Table 2). The corresponding rate of in-lesion binary restenosis was reduced from 32% to 2% ($p < 0.001$).

Clinical outcomes. The clinical outcomes of the patients are listed in Table 3. There were no acute stent thromboses within 24 h after stent implantation. There were five cases of definite (angiographically documented) stent thromboses and one case of possible stent thrombosis. Of the definite stent thromboses, three occurred subacutely and two lately. Only one patient (with late stent thrombosis), who developed allergy to clopidogrel and had received ticlopidine for three months, had discontinued her antiplatelet therapy three months before the episode. Stent thrombosis occurred in five patients, with bifurcational and in one with an ostial lesion. The rate of myocardial infarction was insignificantly different in the two groups (Table 3).

The rate of TLR was lower in the SES group (Table 3). Kaplan-Meier estimates of event-free survival are shown in Figure 2. The results of the subgroup analyses are illustrated in Figure 3, demonstrating a significant difference favoring SES in all subsets of patients also in those previously found to be associated with an increased risk of restenosis after implantation of BMS.

DISCUSSION

We tested the hypothesis that SES would be superior to the corresponding BMS with regard to the angiographic outcome in complex coronary artery lesions. The main result of the SCANDSTENT study was a marked reduction of neointimal hyperplasia in patients who had one or more SES implanted. Despite the complex nature of all the lesions included in the study, the MLD at follow-up in the bare-metal stent group was of the same magnitude as in previous trials of less complex lesions. Our study was powered to detect a difference in MLD of at least 0.25 mm

Table 3. Major Adverse Cardiac Events During Seven Months of Follow-Up

	% of Patients		
	Sirolimus-Eluting Stent (n = 162)	Bare-Metal Stent (n = 157)	p Value
Death	0.6*	0.6	1.0
Myocardial infarction			0.28
STEMI	0.6	1.2	
NSTEMI	0.6	1.9	
Target lesion revascularization in subgroups			
Occlusions, n = 115	0	32.1	
Bifurcations, n = 109	7.1	29.4	
Ostial lesions, n = 73	0	35.1	
Angulations, n = 25	0	0	
Total	2.5	29.3	<0.001
Any MACE	4.3	29.9	<0.001
Stent thrombosis	0.6*	3.1	0.12

One sudden death (possible stent thrombosis).

MACE = major adverse cardiac event; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

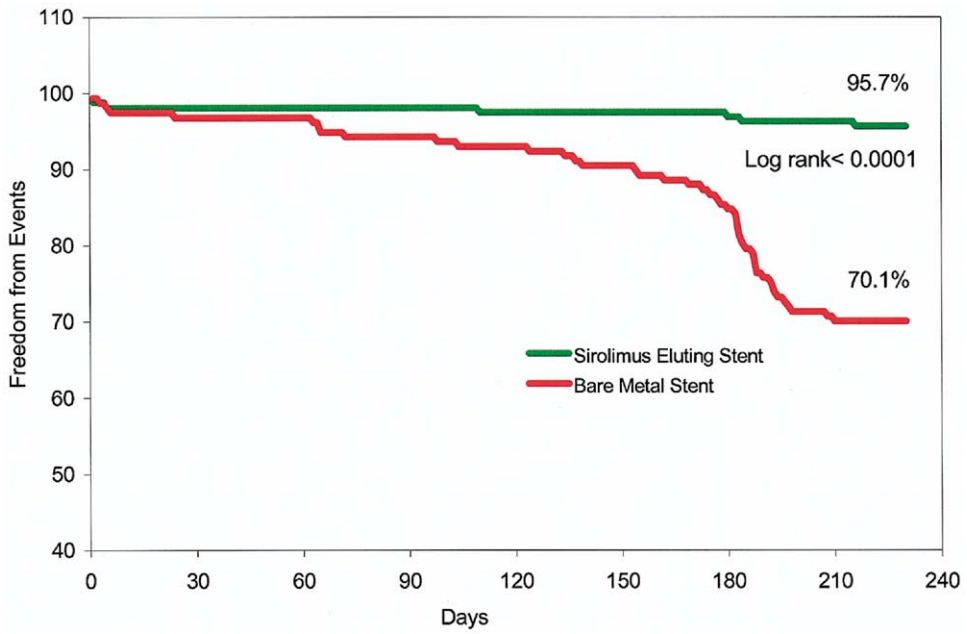

Figure 2. Kaplan-Meier estimates of event-free survival among patients who received sirolimus-eluting and bare-metal stents.

between the two groups, a difference that was markedly exceeded.

Comparison with other studies. Our results demonstrated a 90% relative reduction in the rate of restenosis in patients who had SES implanted in comparison with the corresponding stent without drug-eluting properties. This markedly reduced restenosis rate was of the same magnitude as that found in other drug-eluting stent studies despite a higher level of lesion complexity in our patients. Whereas the frequency of TLR of less complex lesion types are usually lower than the angiographic restenosis rate (13,14,16), most of our patients with angiographic restenosis were treated with a repeat angioplasty because of recurrence of symptoms. This discrepancy may reflect a more pronounced clinical importance of the development of restenosis in a complex than in a simple coronary lesion.

The mean pretreatment diameter stenosis of the lesions in the present study was considerably higher than in other studies, which is explained by a relatively large fraction of patients with total and subtotal occlusions. Randomized studies of the treatment of total coronary occlusions have demonstrated a reduction in the restenosis rate from approximately 70% in the balloon-treated groups compared with a variety of 30% to 55% in the stent groups dependent on lesion complexity, with a corresponding reduction in the need for revascularization and with no increased risk of stent thrombosis (18–20).

No randomized studies have been published comparing drug-eluting and BMS implantation in lesions located in bifurcations. A small randomized comparison of stenting or not stenting the side branch with SES showed improved results compared with historical BMS controls with regard to the rate of restenosis but did not give a solution to the problem (21).

Patients with lesions located in bifurcations were included in the SCANDSTENT study provided the side branch had a diameter that allowed stent implantation in most cases. With the only restriction that all vessels should preferably stay open after the procedure, the side branches were treated at the discretion of the operator. We found considerably better angiographic results after implantation of SES compared with BMS in the main branches of the bifurcations, and although the operators chose to implant stents in only slightly more than half of the side branches in both groups, the angiographic results of the side branches alone were considerably better in the SES group. Accordingly, the rates of TLR of the side branches were significantly higher in the BMS group.

That stent implantation gives better results compared with balloon angioplasty in ostial lesions of the left anterior descending artery have been reported previously (22). In addition, the implantation of SES in ostial lesions seems to improve both clinical and angiographic outcome compared with treatment with conventional BMS (23). Both ostial and tortuous lesions have been excluded from previous randomized drug-eluting stent trials. The SCANDSTENT study demonstrates significantly better results with SES compared with BMS in these complex lesions.

Predictors of restenosis. Some other important predictors of restenosis, the presence of diabetes mellitus and the length of the treated lesions, have to be considered (5,7,14,24). Compared with other studies, our patient population had a slightly lower frequency of diabetic patients in both groups, whereas our patients had considerably longer lesions than those treated in previous trials. Subgroup analyses of our patients showed a consistent benefit of SES on TLR. That the risk factors of developing restenosis after BMS implantation turned out to be of limited value in

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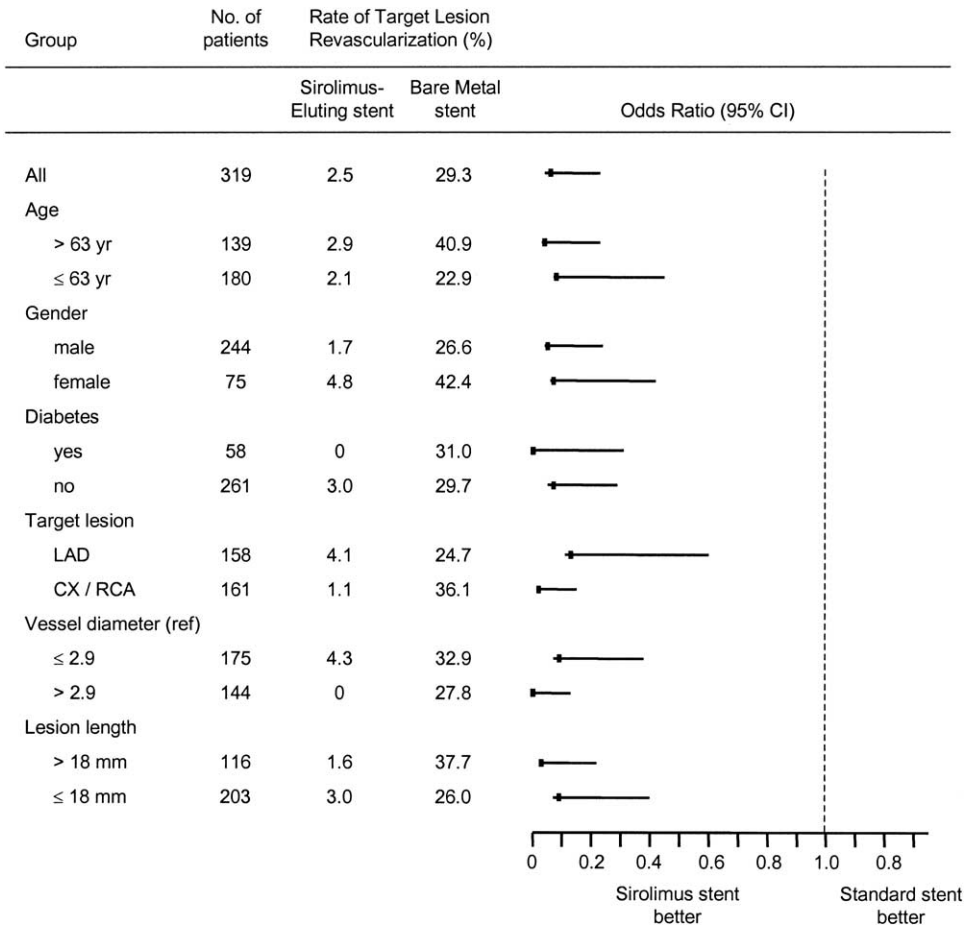

Figure 3. Subgroup analysis for the six-month rate of target lesion revascularization. CI = confidence interval; CX = circumflex; LAD = left anterior descending; RCA = right coronary artery.

patients treated with SES calls for a revision of these risk factors in the new stent era. Among lesion types, all except angulated lesions had a similar benefit of SES stenting.

Stent thrombosis. The rate of stent thrombosis in the present study was of the same magnitude as those reported in previous trials of BMS treatment of less complex lesions (13–16). In two meta-analyses, the rate of stent thrombosis after drug-eluting stent implantation was <1% (25,26) and, in a large registry, the rate was 2.6% after implantation of BMS and 1% after drug-eluting stents (27). Accordingly, most of the stent thromboses occurring in our study were observed in the BMS group. A low rate of stent thombosis in our SES patients could be caused by selection bias. However, Jeremias et al. (28) found a <1% rate of stent thrombosis in a consecutive series of SES implantations that involved 20% of bifurcations. Diabetes was present in 37% of their patients, whereas the frequency of diabetes in our study was lower. The results of the present study revealed that SES can be used in a high fraction of "everyday patients" without further risk of adverse events. Because all definite cases of stent thrombosis occurred in patients who had BMS implanted in bifurcation lesions, we recommend that implantation of BMS in such lesions is carefully considered.

Study limitations. A methodological limitation of the present study was the open design of the treatment, implicating that both operators and patients were aware of the nature of the implanted stents. Accordingly, a certain bias in both patients' and physicians' interpretation of symptoms at follow-up might be expected. However, it is highly unlikely that this knowledge of stent types should have had any impact on the development of angiographic changes, which were analyzed blindly. Furthermore, all clinical end points were adjudicated by a blinded clinical events committee, that found only two cases in which the operator, contrary to the core laboratory, judged the lesion severity as to necessitate revascularization. Although the results of the SCANDSTENT study broaden the indication for implantation of drug-eluting stents, only long-term follow-up of the patients will ensure the durability of these initially promising results (29–31).

Conclusions. In conclusion, implantation of SES results in improved angiographic and clinical results compared with BMS in certain complex coronary artery lesions. The superior results are not associated with any increase in the occurrence of stent thrombosis.

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